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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,907	BOGEN ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,77,83-94,97-108 and 118-123* is/are pending in the application.

4a) Of the above claim(s) *1-37,77,84-87,93,94,97 and 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83,88-92,98-100 and 118-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/16/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-37, 77, 83-94, 97-108, and 118-123 are all the pending claims for this application.

2. Claims 1-37, 77, 84-87, 93, 94, 97, 101-108 are withdrawn from examination.

3. Claim 95 was cancelled and Claim 83 was amended in the Response of 2/16/09.

4. Claims 83, 88-92, 98-100 and 118-123 are all the pending claims under examination with targeting units for a ligand species of soluble CD40 ligand and the chemokines, RANTES and MIP-1α, and the species of antigenic units for an antigenic scFv.

5. This action is FINAL.

Information Disclosure Statement

6. The IDS of 2/16/09 has been considered and entered. The examiner's initialed and signed copy of the 1449 is attached.

Withdrawal of Objections

Claim Objections

7. The objection to Claims 83 and 95 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is moot in view of cancelled Claim 95.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

8. The rejection of Claims 88-92 and 98 because they are drawn to a targeting unit that can recognize a corresponding binding partner on a broader genus of cells than an APC of generic Claim 83 is withdrawn.

Applicants allegations on pp. 17-18 have been considered and are persuasive. Applicants allege "While there are some ligands present on both APCs and non-APCs, Claim 83 and claims dependent thereon recite ligands that bind to APCs. One of ordinary skill in the art would readily recognize such a difference and would understand that Claim 83 and the ligands recited in Claims 88-92 and 98, i.e. soluble CD40 or a chemokine to be species of targeting units that are capable of binding to an APC."

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

9. The rejection of Claims 118 (and 120) under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained for reasons of record as set forth in the Office Actions of 11/7/06, 7/19/07, 4/10/08 and 11/18/08.

In the Office Action of 7/19/07, the Examiner stated that the specification is not enabling for the full scope of the claims because:

"The specification does not teach gene immunization (or gene therapy) methods for treating or *preventing* a cancer much less a myeloma or lymphoma or inducing a *prophylactic* T- or B-cell immune response in a *human patient* with a *nucleic acid* of the claims examined in the Office Action of 11/7/06, the vector comprising the nucleic acid or a vector-transfected cell or cell line encoding the recombinant antibody-based molecule. There are no working examples in Applicant's specification to guide the skilled artisan in practicing the administration of the nucleic acid, vector or transfected host cell, more especially by injection and electroporation, which results in *a) induction of an immune B- and T cell response or b) a reduction in a cancer such as myeloma or lymphoma*. The goal of tumor vaccination is the induction of tumor immunity to *prevent* tumor occurrence or recurrence and Applicants have not demonstrated any such effect(s) with the nucleic acid as originally examined."

In the Office Action of 4/10/08, the Examiner maintained the rejection as follows:

"a) Applicants' allegations on pp. 18-24 of the Response of 1/22/08 and copies of the cited references (Stevenson (2004); Eisen (1968); Schulenburg (1971); Eisen (1985); Brunsvik [*actually Fredriksen (Examiner's correction)*] (2007); Schjetne (2007); and Fredriksen (2006)) have been considered and are not found persuasive.

Applicants allege the claims are fully enabled for the scope of Vaccibody embodiments because: expression product for specific Vaccibody protein to idiotypic Fv from the murine MOPC315.4 tumor (i.e., the antigenic unit is an idiotype derived from the murine multiple myeloma MOPC315.4 cell line) was detected in sera of mice (Example 5 on pp. 34-35 of the specification); methods for using the pharmaceutical compositions to treat and prevent myeloma showing intra-muscular injection and electroporation for expression in vivo (p. 28 of the specification and Examples 5 and 6; citing Stevenson (2004) as support for established route of injection); the murine MOPC315.4 multiple myeloma animal model is correlative and predictive for treatment and prevention of multiple myeloma in other animals (citing Eisen (1968), Schulenburg (1971) and Eisen (1985)); the term "vaccine connotes prevention and/or diminishment of a disease in comparison to no vaccine at all"; the specification describes procedures for administering Vaccibody to produce a protective effect and the generation of a protective effect against development of tumors (Figures 21a and 21b; 22 and 23); and further evidence of prophylactic and preventative effects of the pharmaceutical and vaccine compositions (Brunsvik [*actually Fredriksen (Examiner's correction)*] (2007); Schjetne (2007); Fredriksen (2006)).

Examiner's Reply

The Examiner appreciates the detailed explanation, the copies of the reference articles, and the technical effort into characterizing a single vaccibody embodiment, namely, that for generating an anti-idiotypic response against the monoclonal antibody-producing murine MOPC315.4 multiple myeloma in the mouse model in vivo in the specification, and the addition studies for Id vaccines described in the references.

Applicants have established the credibility of the murine MOPC315.4 multiple myeloma mouse model;

Applicants have established with the Id Vaccibody, that a prophylatic and therapeutic effect could be generated against the mouse MOPC315.4 tumor in vivo to block tumor progression by generating an anti-idiotypic response with the VH/VL idiotype of the Vaccibody.

Schjetne (2007) establishes that a clonotypic CD40-expressing tumor in mice could be targeted with Ig-like vaccine construct directed against CD40;

Fredriksen (2006) appears to be the publication of the data presented in the instant specification; and

Fredriksen (2007) establishes that a clonotypic tumor in mice (B lymphoma (A20)) or MOPC315) could be targeted with an Ig-like vaccine construct targeting MIP-1alpha and RANTES.

Notably and significantly, Applicants have not shown that the similar results for generating an anti-idiotype response that was both therapeutic and prophylactic could be generated against for example a human xenograft of multiple myeloma or lymphoma cells in an animal model. Further, Applicants have not shown that the myriad combinations of antigenic units and targeting units for a single monomeric unit encompassed by the claims have actually been used in a construct, administered to an animal model bearing any relevant disease much less multiple myeloma or lymphoma in order to generate a) both a T-cell and B-cell immune response, b) an immunologically effective response against MM or lymphoma, where the response was therapeutic and/or preventative.

The examiner submits that one of ordinary skill in the art could not reasonably make the correlation or prediction that from a single animal model using a single clonotypic tumor with a single Vaccibody, that any Vaccibody embodiment could be used in vivo to treat or prevent any disease much less multiple myeloma in any animal including a human. Applicants' entire presentation does not provide sufficient enablement to practice the scope of the inventive claims.

Examiner draws Applicants attention to the critically important work of Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{8}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not even necessarily correlate with results expected in human multiple myeloma or lymphoma.

For all of the foregoing reasons, this aspect of the rejection is maintained.

b) Applicants' allegations on pp. 24-25 of the Response of 1/22/08 have been considered and are found persuasive.

Applicants' admission on the record is that the "dimmers" ["dimers"] in the present application are formed from homodimers, which assemble spontaneously from the expression products of one single vector (due to the presence of the dimerization unit in the monomers). It should be noted that only expression of one vector is necessary in order for the claimed embodiments to work."

In the Office Action of 11/18/08, the rejection was maintained as follows:

"Applicants' allegations on pp. 13-16 of the Response of 7/10/08 have been considered and are not found persuasive. Applicants allege "With respect to Claim 118, the claim language merely requires that the isolated nucleic acid fragment of Claim 83 be formulated "to be administered to a patient to induce production of said antibody based dimeric molecule" and that the injection of the isolated nucleic acid molecule in a "patient" leads to production in the patient of the expression product of the isolated nucleic acid molecule. Hence, Claim 83 does not require that the patient raise an immune response against the expression product. Finally Applicants allege the art pertaining to nucleic acid vaccination, has amply demonstrated that expression of an injected nucleic acid molecule can be easily accomplished.

Response to Arguments

In the interest of expediting prosecution, all of the examiner's foregoing comments are re-iterated and incorporated in full. Arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03). Further, Applicants assertion that the general state of the art for nucleic acid vaccination is enabled is not supported by extrinsic evidence. Pursuant to MPEP 2144.03, "ordinarily there must be some form of evidence in the record to support an assertion of common knowledge."

Applicants are invited to supplement the record with extrinsic evidence to support the argument that any nucleic acid vaccination much less the full scope of the claims is enabled. Alternatively, Applicants are invited to amend the claims to read on what is reasonably enabled by the specification in using the nucleic acid to generate expression of the dimeric antibody molecule in vivo. The examiner submits that one of ordinary skill in the art could not reasonably make the correlation or prediction that from a single working animal model using a single example of a nucleic acid encoding a single Vaccibody embodiment in the specification, that any nucleic acid encoding any Vaccibody meeting all of the instant claim limitations (i.e., to the extent they are encompassed in Claim 83) could even be expressed or to what measurable extent the Vaccibody could be expressed in vivo. Applicants' entire presentation thus far does not provide sufficient enablement to practice the full scope of the inventive claims."

Applicants allegations on pp. 13-17 of the Response of 2/16/09 have been considered and are not found persuasive. Applicants allege "The claims merely require that upon administration of the isolated nucleic acid of Claim 83 to a patient the isolated nucleic acid induces production of the recombinant antibody-based dimeric molecule in vivo"; Kutzler, M. et al. (Nature Reviews Genetics(9): 776-788 (2008)) describes the technology encompassed by DNA vaccine technology noting in particular: "In the past decade and a half, the DNA vaccine concept has been tested and applied against various pathogens and tumour antigens. In theory, this conceptually safe, non-live vaccine approach is a unique and technically simple means to induce immune responses"; Tang, De-Chu et al. (Nature 356:152-154 (1992) (abstract)) discloses production of an immune reaction to a foreign protein by genetic immunization of the gene encoding the protein into the skin of mice"; Wang et al. (1998) (abstract) discloses a DNA vaccination methodology against malaria. Human patients were immunized with a plasmid vector encoding a malaria protein. These patients developed antigen-specific CD8+ T-cell responses. More importantly, all 10 peptides tested resulted in immune responses that were restricted by six human lymphocyte antigen (HLA) class I alleles; and MacGregor, R.R. et al. discloses human DNA vaccination using an effective HIV-1 construct that induced robust T-cell responses. "Our results demonstrate induction of a

CD4 Thl type response following DNA vaccination when HIV-1 expression vectors are administered as plasmid vaccines." MacGregor, at page 2141."

Response to Arguments

Initially, the examiner submits that Applicants are incorrect in their understanding of the law for enablement under 35 U.S.C. 112, first paragraph. The specification must be enabling for making and ***using*** the invention. Applicants' assertion that the expressed recombinant antibody-based dimeric molecule encoded by the nucleic acid is not required to have a function much less an ability to target or bind an antigen, or that the nucleic acid as claimed does not require the antibody-based dimeric molecule product to have any function, is a legal falsehood. The same antibody-based dimeric molecule generated from the nucleic acid must have a utility, otherwise what purpose would be served by formulating the nucleic acid for administration to a patient in order to induce production of the product?

Under MPEP 2138.05 and *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) "To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. "[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [ ] this may require successful testing of the product." As for the instant claimed nucleic acid, Applicants have not demonstrated that the product could be successfully expressed much less that the product would be functional insofar as whether the monomer unit would actually

dimerized with a corresponding monomer unit or much less where the antigenic and targeting units of each monomer are themselves required to be functional.

The four (4) cited references have been considered for their enabling disclosure at the time of application filing for DNA vaccine therapy. Notably, none of the references teaches examples of an expression product from a DNA vaccine having any where near the complexity on the instant claimed molecule. The examiner relies on the decision from *Ex parte Murphy and Burford* (217 USPQ 479 (BPAI 1982)) stating in part:

> "The determination that a reference is from nonanalogous art is therefore two fold. First, we decide if the reference is within the field of the inventor's endeavor. If it is not, we proceed to determine whether the reference is reasonably pertinent to the particular problem with which the inventor was involved."

The field of art for the references is within the field of the inventor's endeavor (DNA vaccines), however, the references are not considered pertinent to the particular problem the invention is alleging solving (expression of a monomeric unit comprising an functional antigenic unit and a functional targeting unit, where the monomer is constructed such that it is required to form a pairwise association with another corresponding and expressed monomer). None of the references teach a monomer bearing any resemblance to the instant claimed monomer nor do they require that two monomers are expressed from different nucleic acids in vivo or that two expressed monomers would form a pair in vivo and possess functional activity.

The rejection is maintained because Applicants have not met their burden in responding to the outstanding grounds for rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. The rejection of Claims 83, 88-92, 98-100, and 118-123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003; cited in the PTO 892 form of 11/7/06) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 11/18/08 as follows:

"Claims 83, 88-92, 95, 98-100, and 118-123 are *interpreted* as being drawn to a nucleic acid encoding a monomeric unit for recombinant antibody-based dimeric molecule, wherein each monomeric unit comprises a targeting unit for binding an APC, a dimerization motif and an antigenic unit all being operably linked, where the dimerization motif comprises an Ig hinge and a Cgamma3 domain (and no CH2 domain) and the dimerization motif of each monomer contributes to the dimerization by disulfide bonding between the Ig hinge and hydrophobic interactions between the Cgamma3 domains (Claims 83 and 95), where the targeting unit is a ligand (Claim 88) comprising soluble CD40 ligand (Claims 89) or a chemokine (Claims 89) such as RANTES or MIP-1α (Claims 90-92), where the targeting unit can target a chemokine receptor (Claim 98) and the antigenic units is an antigenic scFv with the VH and VL from a monoclonal Ig produced by a myeloma or lymphoma (Claims 99 and 100), and the nucleic acid is formulated for administering to a subject (Claim 118), and vectors comprising the nucleic acid (Claim 119), and a cell line transfected with the vectors (Claim 120), and compositions comprising the nucleic acid, the vector or the cell (Claims 121 and 122) and a kit comprising the nucleic acid to produce the antibody-based molecule (Claim 123).

Herman discloses nucleic acids, vectors comprising nucleic acids and vector transfected cell lines encoding a multispecific ligand comprising at least two different binding specificities for different target ligands comprising any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including tetraspecific antibody formats and fusions of the antibody to other functional moieties (eg. toxins, cytokines, chemokines, streptavidin, adhesion molecules) [0107-0108], where the multispecific ligand comprises an Fc portion and an Ig hinge portion. An Fc portion may be a partial Fc portion (eg. minibody-CH3) [0069]. The amino acid composition (including length) of the hinge portion should provide means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper, fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide bonds eg. IgG3) [0116]. The binding characteristics of the multispecific ligand e.g., scfv, is that the target ligand is of sufficient affinity to effectively bind or remain bound without the other unit being available for simultaneous binding [0119]. An example of one monomer comprises a first ligand moiety which recognizes a first target ligand that is over-expressed on a disease associated entity (for example a diseased or disease-causing or mediating cell or infectious agent) and a second ligand binding moiety that recognizes a target ligand and wherein the

first target ligand is characterized in that it does not lend itself to facilitating or permitting internalization of the second ligand binding moiety [0122].

Herman discloses the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a ligand which effects binding to another immune cell, for example a T cell or APC. The multispecific ligand is a tetraspecific antibody or the first moiety binds to but is incapable of modulating the activity of an immune cell and the second moiety modulates the activity of the immune cell independently of the first moiety [0137].

Herman discloses a multispecific ligand which comprises a first ligand binding moiety which neutralizes a ligand eg. a natural ligand such as a chemokine and a second ligand binding moiety which binds to a cell marker associated with a cell [0138]. Examples of proteins which are targeted by multispecific ligand (targeting unit) include CD40 [0164], MIP-1 alpha and RANTES [0428]. Herman discloses a multispecific ligand comprising an anti-idiotype antibody (antigenic unit) so as to facilitate a desired immune response eg. vaccination type responses [0172, 0252]. For one embodiment, Herman discloses a multispecific ligand containing an immunocytokine containing an anti-idiotypic antibody component and a cytokine component [0018]. Herman discloses nucleic acids, expression vectors and host cells expressing the vectors to produce a multispecific ligand [0241- 0298; 0314-0319]. Herman discloses a kit comprising one or more polynucleotides comprising one or more DNA sequences, where the DNA sequences encode one or more polypeptides which are sufficient to constitute a multispecific ligand as defined in any of the preceding paragraphs [0424]."

Applicants' allegations on pp. 19-22 of the Response of 2/16/09 have been considered and are not found persuasive. Applicants allege Herman fails to teach or suggest a targeting unit and a antigenic unit in the monomer unit which are separated by a dimerization motif and wherein the monomer units each lack a CH2 domain. The constructs in Herman are devised to have an antibody units (a VH, VL F(ab')2, Fab, Fab', Facb, Fc,) on the same side of a *dimerization motif and hinge region*. Applicants respectfully submit that all of the claim elements of the amended 83 must be found in Herman as arranged in the rejected claim."

Response to Arguments

Initially, Applicants allegation that Herman teaches constructs devised to have antibody units on the same side of a dimerization motif and hinge region is not supported by citation to a specific paragraph and line number in the reference. The examiner has not identified when Herman teaches this and only this design construct.

Secondly, Applicants appear to be confused in their own understanding of the claimed invention. Throughout examination, it has been understood that the dimerization motif and hinge region where the same or at least the hinge portion was part of the dimerization motif. Now, Applicants would have the Office believe that the dimerization motif and the hinge are separate parts of the monomer. In this case, the monomer would then comprise two hinge regions plus Cγ3. Applicants interpretation is inconsistent with the prosecution proceeding and is not incorporated into the claims, and if this is the intended design of the monomer, then Applicants are invited to amend the claims as such.

Thirdly, the examiner submits that the amended claims are interpreted as being drawn to nucleic acid encoding a monomer comprising the targeting unit – dimerization motif (Ig hinge *and* Cγ3)- antigenic unit or antigenic unit- dimerization motif (Ig hinge *and* Cγ3)- targeting unit. Herman teaches all of the elements for designing such a construct, for example, fusion proteins comprising a immunocytokine having an anti-idiotypic antibody component and a cytokine component fused therewith or conjugated thereto, or ligands including bispecific antibodies, antibody fusions/ conjugates eg. where the immune affecting antibody portion or other moiety is conjugated, fused etc. to an antibody or fragment that binds to an entity associated marker [0223]. Herman teaches making a "divalent immunoconjugate" by attaching therapeutic agents to a carbohydrate moiety and to a free sulfhydryl group [0338]. Accordingly, Herman teaches an example of a bispecific antibody comprising two dAb components comprising linked via a linker having at least part of a constant region for fusion for example to a toxin (eg. at least a

partial hinge region, and preferably also at least a partial CH2 domain (optionally also at least a partial CH3 domain) [0345]. Herman requires the hinge region, does not necessarily require the CH2 domain although preferable, and may include the CH3 domain, which is considered to read on the constructs in view of all of the other elements taught (and discussed above) by Herman as possible combinations for constructs. The rejection is maintained.

New Grounds for Objection

Claim Objections

11. Claims 120 and 121 are objected to because they reference two sets of claims drawn to different features (MPEP 608.01(n)).

Conclusion

12. No claims are allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority